(l'Hôtel-Dieu de Gaspé) and Dr J.-P. Breton (ministère des Affaires sociales, division des maladies infectieuses) for supplying the serum samples and clinical histories. In addition, we are grateful to D. Archambault, M. St-Louis and C. Th'ng for technical assistance.

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Verapamil and supraventricular tachyarrhythmias: beneficial effect in patients with chronic pulmonary disease

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Patients with supraventricular tachyarrhythmias that do not respond to initial therapeutic measures present a familiar and challenging clinical problem. The papaverine derivative verapamil (Isoptin, Pentagone Laboratory Ltd., Montreal) — α-isopropyl-α-[(N-methyl-N-homoveratryl)-γ-aminopropyl]-3,4-dimethoxyphenylacetonitrile hydrochloride — has been reported to be effective in the treatment of supraventricular tachyarrhythmias.[1-4] Although the exact mechanism of its antiarrhythmic action is not completely understood, verapamil has aroused great interest because it appears to exert its effects on a basis different from that of other antiarrhythmic agents.[5-9]

In this report we outline our experience with the use of verapamil in patients with supraventricular tachyarrhythmias that were difficult to control with usual therapeutic measures, and identify a subset of patients with chronic lung disease and atrial flutter in whom the drug appears to be highly effective.

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Criteria for verapamil therapy and results

Eleven patients, nine men and two women aged 52 to 72 years, with symptomatic supraventricular

tachyarrhythmias that were difficult to control received verapamil (Table I). The criteria for verapamil administration were the following:

- Arrhythmia of more than 24 hours' duration. (In all the patients except nos. 7 and 10 the arrhythmia had been present for 48 hours or more.)
- Unsatisfactory response to traditional pharmacologic therapy over this period. (All the patients had received digoxin except one [no. 10], in whom digoxin had not been effective on previous occasions, and at least one other agent — either quinidine or disopyramide.)
- Symptoms or hemodynamic consequences of the arrhythmia that required further treatment.

Verapamil was usually administered intravenously in 5-mg doses every 5 minutes until a satisfactory response or a total dose of 25 mg was reached. With this approach the effect was usually seen within 5 minutes of administration of the second dose.

The patients could be classed into two groups on the basis of clinical diagnosis. Five patients (nos. 1 to 5) had a long history of chronic

Table I—Patient characteristics and response to verapamil therapy

Patient no.	Age(yr) and sex	Clinical diagnosis	Arrhythmia	Previous unsuccessful treatment	Dosage of verapamil	Response	Adverse effects	Outcome
1	72, M	Chronic obstructive lung disease	Atrial flutter	Digoxin, quinidine	10 mg IV (5 mg q 10 min)	Sinus rhythm	None	Sinus rhythm maintained
2	65, M	Chronic obstructive lung disease, pneumonia	Atrial flutter	Digoxin, quinidine, rapid atrial pacing	10 mg IV (5 mg q 5 min)	Atrial fibrillation	None	
					15 mg IV (5 mg q 5 min)	Atrial fibrillation	None	
					80 mg po q8h	Sinus rhythm	None	Sinus rhythm
3	64, M	Chronic bronchitis, alcoholism, pneumonia	Atrial flutter	Digoxin, quinidine	5 mg IV	Transient sinus rhythm	None	
					25 mg IV (5 mg q 5 min)	Sinus rhythm	None	Sinus rhythm
4	65, M	Chronic obstructive lung disease, acute respiratory failure	Atrial flutter	Digoxin, disopyramide	10 mg IV (5 mg q 10 min) 5 mg IV (q4-6h)	Slowing of ventricular rate	Hypotension	Atrial fibrillation controlled with digoxin after recovery from acute respiratory failure
5	52, M	Chronic obstructive lung disease, acute bronchitis	Atrial flutter	Digoxin, disopyramide	5 mg IV 5 mg IV (qh x 2)	Slowing of ventricular rate	None	Sinus rhythm
6	54, M	Heart failure, cause unknown (probably cardiomyopathy)	Atrial fibrillation	Digoxin, propranolol, quinidine	25 mg IV (5 mg q 5 min)	Sinus rhythm None	Hypotension (blood pressure fell from 130/70 to 40/25 mm Hg); required dopamine	Ventricular rate controlled with digoxin, 10 mg po, and propranolol, 160 mg per day
7	70, M	Chronic lymphocytic leukemia, *Pneumocystis carinii* pneumonia	Atrial fibrillation/ flutter	Digoxin, propranolol	20 mg IV (5 mg q 5 min)	None	None	Died
8	66, M	Myocardial infarction	Atrial tachycardia	Digoxin, quinidine	10 mg IV	Sinus rhythm	None	Sinus rhythm
9	67, F	Mitral stenosis	Atrial tachycardia	Digoxin, quinidine, propranolol	25 mg IV (5 mg q 5 min)	Slowing of ventricular rate	None	Recurrent arrhythmias despite verapamil therapy
					480 mg po/d	Recurrent arrhythmias		
10	65, M	None	Paroxysmal supraventricular tachycardia	Phenylephrine, edrophonium chloride, quinidine	10 mg IV (5 mg q 5min)	Sinus rhythm	None	Sinus rhythm
11	69, F	Ischemic heart disease	Paroxysmal supraventricular tachycardia	Edrophonium chloride, vasopressors, digoxin, propranolol	5 mg IV	Sinus rhythm	Transient atrioventricular block	Recurrent arrhythmias despite oral digoxin and verapamil therapy
					80 mg po q4h	Recurrent arrhythmias	None	Radiofrequency pacemaker and coronary sinus catheter system installed

obstructive lung disease, which was usually severe, as indicated by the results of pulmonary function tests (Table II), were hypoxic and had atrial flutter with a rapid ventricular response. Treatment with verapamil was very effective in these patients. Three responses were noted: conversion to sinus rhythm (Fig. 1), conversion to atrial fibrillation with a slower ventricular response (Fig. 2) and slowing of the ventricular rate.

Hypotension, the only adverse effect seen, occurred in the sickest patient (no. 4), who was receiving mechanical ventilation for acute respiratory failure. The hypotension was of short duration, in contrast to the electrophysiologic effect: the maximum slowing of the ventricular rate usually lasted 30 to 60 minutes.

The six patients (nos. 6 to 11) constituting the second group presented with various clinical problems. Sinus rhythm was restored in three patients, one of whom (no. 11) had transient atrioventricular block before sinus rhythm resumed (Fig. 3). Control of the ventricular rate was achieved in one patient, and no effect was observed in the remaining two patients. Profound hypotension, occurring in one patient (no. 6), was the only significant complication in this group.

Discussion

This study has identified a subgroup of patients with chronic obstructive lung disease and atrial flutter whose arrhythmia responded well to intravenously administered verapamil. Previous studies of the effect of verapamil in the treatment of atrial flutter have considered almost exclusively patients with ischemic or rheumatic heart disease.

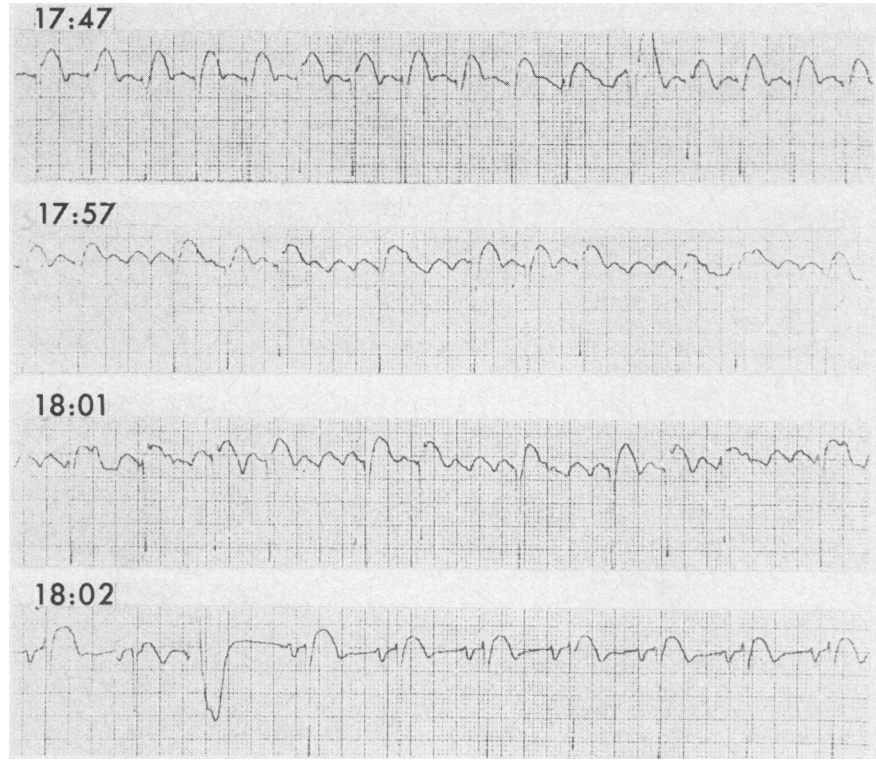

FIG. 1—Tracings of modified lead V_1 showing atrial flutter in patient 1 at time first (top panel) and second (next panel) 5-mg doses of verapamil were given. Sinus rhythm restored 5 minutes after second dose was received, at which time occasional ventricular ectopic beats were observed.

Table II—Pulmonary function and blood gas data for patients with chronic obstructive pulmonary disease (group 1)

Variable	Patient no. 1	2	3	4	5
Time before arrhythmia, yr	6	5	1	0.1 (after)	0.5
Vital capacity, l (and % of predicted value)	4.37 (119)	2.71 (65)	1.95 (50)	2.50 (62)	2.60 (65)
Maximum mid-expiratory flow, l/s (and % of predicted value)	0.94 (35)*	0.69 (15)	1.70 (41)	0.40 (13)	1.50 (17)†
Forced expiratory volume in 1 s (and % of forced vital capacity)	–	–	1.50 (77)	0.85	0.61 (23)
Residual volume, l (and % of predicted value)	–	3.53 (174)	3.31 (144)	–	5.19 (276)
Partial pressure of oxygen in arterial blood with patient breathing room air during function tests, mm Hg	–	–	53	–	–
Arterial blood gas values with patient breathing room air before verapamil administration					
Partial pressure of oxygen, mm Hg	60	51	–	28‡	47
Partial pressure of carbon dioxide, mm Hg	34	42	–	64	55
pH	7.51	7.53	–	7.37	7.37
Bicarbonate, mmol/l	26.6	34.6	–	35.0	28.6

*When bronchodilators were used an increase was observed.
†When bronchodilators were used no response was observed.
‡The patient received mechanical ventilation.

Although the type of arrhythmia is a critical determinant of the efficacy of any drug, this study raises the question whether the clinical circumstances may be of additional importance for the use of verapamil. Despite the paucity of clinical data, experimental data support the contention that verapamil could have a beneficial effect in patients with obstructive lung disease who have had a recent pulmonary insult. Verapamil blocks excitation coupling of smooth muscle and could induce relaxation of bronchial smooth muscle.[7] Also, contraction of tracheal smooth muscle induced by metabolic derangement can be blocked by a calcium antagonist such as verapamil.[10]

Regardless of the role verapamil may play in the treatment of lung disease, its use has advantages in patients that have chronic lung disease with recent pulmonary deterioration and atrial flutter. Atrial flutter is often difficult to treat pharmacologically. The ideal method of treatment is cardioversion if reversion to normal sinus rhythm is desirable; the probability of persistent sinus rhythm is high. However, because the sedation required prior to cardioversion may pose some risk to patients with severe chronic pulmonary disease, pharmacologic agents should be tried first. Unfortunately, initial treatment with digitalis compounds may increase the risks of complications during subsequent attempts at cardioversion. The presence of obstructive lung disease limits the use of other drugs, specifically the β-adrenergic blocking agents. Verapamil may become the preferred agent in this situation because of its efficacy, short duration of action that does not limit the possibility of later cardioversion, and the absence of an adverse effect on airways resistance.

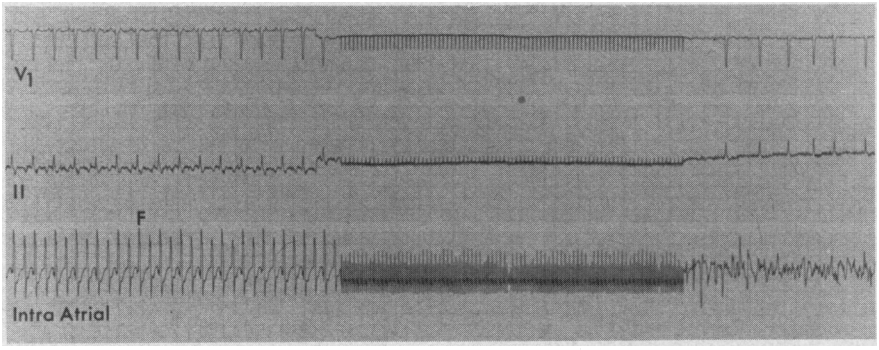

FIG. 2—Tracings of leads V_1 and II and simultaneous intra-atrial recording (paper speed 5 mm/s) for patient 2 after 10 mg of verapamil was given intravenously. Conversion of atrial flutter to atrial fibrillation and transition from regular flutter waves (F) to chaotic fibrillatory activity demonstrated in intra-atrial tracing.

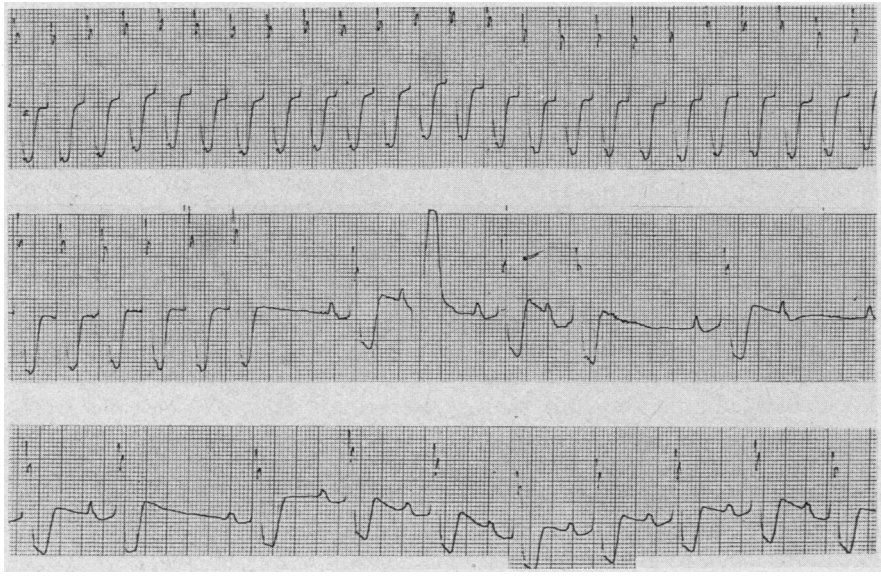

FIG. 3—Tracing of lead V_1 showing supraventricular tachycardia terminating abruptly in patient 11 after 5 mg of verapamil was given intravenously. Transient sinoatrial arrest, atrioventricular block and ventricular ectopic beats seen (left side of centre panel). Right bundle branch block had been present for many years.

The patients in group 2 had different cardiac diseases and arrhythmias. In two patients, one with atrial fibrillation and one with atrial flutter, the arrhythmia failed to respond to verapamil. In other studies of patients with arrhythmias that were less difficult to control, verapamil decreased the ventricular rate in a high proportion of the patients with atrial fibrillation.[2,5] The two patients in our study who had paroxysmal supraventricular tachycardia responded well to verapamil administration. The rate of reversion of paroxysmal supraventricular tachycardia with intravenous administration of verapamil has varied in several reports from 66%[3] to 70%[11] to 97%.[12] We have found, as have others,[1] that when verapamil is administered orally it may not be as effective in the control of paroxysmal supraventricular or atrial tachycardia.

The serious adverse effects of verapamil include hypotension, bradycardia, sinoatrial and atrioventricular block, and asystole.[4,13] The frequency of these complications during wide use of this drug have not yet been estimated. In most reported cases the most serious adverse effects have been associated with the concomitant administration of β-adrenergic blocking agents. Because both drugs are calcium antagonists, though with different mechanisms of action, the effects of the two drugs are additive and perhaps synergistic. The thesis that the adverse effects of verapamil may be minimized by not administering the drug for at least 6 hours to patients who have received β-blocking drugs[3] may not be substantiated; one of our pa-

tients, in whom propranolol was discontinued 48 hours before verapamil was administered, had a hypotensive response. The adverse effects of verapamil can be reversed by atropine, β-agonists such as isoproterenol, intravenously administered calcium or the temporary installation of a cardiac pacemaker.

Verapamil's pharmacologic effects have been attributed primarily to its ability to block the slow inward current (the slow response) across the cell membrane.[7,9] The drug abolishes the increased automaticity seen in some fibres that appears to depend on the slow response. Since both the sinus and the atrioventricular nodes depend on the slow inward current,[7,14] verapamil is a powerful depressor of their activity. Supraventricular tachycardia may result from continuous re-entry of impulses with either the sinus or the atrioventricular node as part of the re-entry pathway. Verapamil can terminate this kind of arrhythmia by interrupting the re-entry pathway and prolonging or preventing conduction through either node. Depression of the atrioventricular node's action potentials and conduction[14,15] is undoubtedly the mechanism by which verapamil decreases the ventricular response in atrial flutter and atrial fibrillation.

The conversion of atrial flutter to sinus rhythm or atrial fibrillation after verapamil is administered is not completely understood. It is not our intention to enter the debate on the respective roles of increased automaticity and re-entry in the genesis of atrial flutter. Verapamil may restore sinus rhythm by suppressing atrial fibres whose diastolic depolarization and automaticity depend on the slow inward current and are responsible for arrhythmias. Alternatively, it may block conduction in a re-entry pathway that involves tissue sensitive to verapamil. The mechanism for the conversion to atrial fibrillation is even more enigmatic because verapamil does not exert any effect on the relative or effective refractory periods of atrial fibres or on the intra-atrial conduction time.[10] The electrophysiologic basis for this conversion of atrial flutter to atrial fibrillation clearly warrants investigation.

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